**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**
**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

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| *In re* Application of: Wold *et al.* | § | Confirmation No. 1203 |
| | § | |
| | § | Group Art Unit: 1632 |
| Serial No.: 09/351,778 | § | |
| | § | Examiner: Priebe, Scott David |
| Filed: July 12, 1999 | § | |
| | § | Atty. Dkt. No.: INGN:109US |
| For: REPLICATION COMPETENT ANTI-CANCER VECTORS | § | |
| | § | |

| CERTIFICATE OF ELECTRONIC SUBMISSION | |
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| DATE OF FILING | December 27, 2006 |

## APPELLANTS' REPLY TO SUPPLEMENTAL EXAMINER'S ANSWER

**Mail Stop Appeal Brief-Patents**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with 37 C.F.R. §41.41 and 37 C.F.R. §41.43(b), Appellants hereby submit this Reply Brief in response to the Examiner's Supplemental Answer dated November 2, 2006. It is believed that no fees are due in connection with this paper; however, should any fees be due the Commissioner is authorized to withdraw the appropriate fees from Fulbright & Jaworski Deposit Account No. 50-1212/INGN:109US.

## STATEMENT OF THE CASE

There is one issue before the Board:

- Whether the two declarations of the inventors ("Wold I"; Exhibit 4 in the appeal brief, and "Wold 2"; Exhibit 5 in the appeal brief) are sufficient under 37 C.F.R. §1.131 to establish invention of the subject matter of claims 10-13, 20-22, 32-44, 60, 61, 64-66, 68, 69, 72-75, 97-99 and 101-108 prior to the effective date of Henderson (U.S. Patent 6,197,293) and Little (U.S. Patent 6,254,862).

Appellants set forth the following response to the Supplemental Examiner's Answer. Appellants will rely on the response set forth in their Appeal Brief and Request for Rehearing to any issues not specifically addressed herein.

### I. The Two Declarations of the Inventors ("Wold I" and "Wold II") are Sufficient Under 37 C.F.R. §1.131 to Establish Invention of the Subject Matter of the Appealed Claims Prior to the Effective Date of Henderson and Little

#### A. Prior Invention Under 37 C.F.R. §1.131 May Be Established Because Appellants Are Not Claiming the Same Patentable Invention as Defined in 37 C.F.R. §41.203(a)

The Examiner agrees with Appellants that prior invention under 37 C.F.R. §1.131 may be established because Appellants are not claiming the same patentable invention as Henderson or Little. More particularly, as set forth in the Supplemental Examiner's Answer dated November 2, 2006, "[t]he Examiner has met with SPE Andrew Wang, an interference specialist in Tech Center 1600, and ***it was determined that there is no potential interference between the instant application and either of the two patents*** [Henderson or Little]." Supplemental Examiner's Answer, page 2 (emphasis added). The Examiner agrees with Appellants that the appealed claims do not anticipate or render obvious the claimed invention of either Henderson or Little.

Supplemental Answer, page 3, last paragraph.[1] ***Therefore, prior invention under 37 C.F.R. §1.131 may be established.***

**B. Appellants Conceived of Their Invention Under 37 C.F.R. §1.131 Prior to the Effective Date of Henderson and Little**

**1. Appellants' Evidence is Sufficient to Demonstrate Conception**

***a) The "Overexpress ADP" Claims: 11-13, 20-22, 32-44, 101-106, and 109***

***(1) The Substantial Evidence of Conception Set Forth by Appellants is Sufficient to Demonstrate Conception***

Appellants have set forth substantial evidence in their appeal brief that they conceived of recombinant adenoviral vectors that overexpress ADP and their use in cancer therapy before March 3, 1997, the earliest priority date of Henderson/Little. This evidence, discussed in detail in the appeal brief (see pages 16-18), is briefly summarized as follows:

- The inventors conducted studies on the E3 transcription region of adenovirus in an effort to understand the function of the various proteins encoded by that region. Wold I, ¶5, citing to Exhibit A.
- The inventors found that mutant adenoviruses that have portions of the E3 region deleted, other than the gene for ADP, produced larger plaques than wild-type adenovirus and produced plaques at different rates than wild type adenovirus. Wold I, ¶5, citing to pages A2-A17 of Exhibit A.

[1] Appellants disagree with the Examiner's assertion that the claims of Henderson or Little, "when read in light of their supporting description, anticipate or render obvious the appealed claims..." Supplemental Answer, page 3. The Examiner appears to be relying on an incorrect standard for determining whether an interference exists. In particular, it appears to Applicants that the Examiner erroneously argues that Applicants' claims must be anticipated or rendered obvious by the other party's ***specification*** rather than the ***claimed subject matter***. Further, even if the Examiner had applied the correct standard by comparing the Henderson and Little claims to Appellants' claims, the Henderson and Little claims would nevertheless not have anticipated Appellants' claims. Applicants have set forth a detailed analysis in their Request for Rehearing that was submitted on March 24, 2006. See, in particular, pages 10-13 of the Request for Rehearing.

- The inventors found that an E3 deletion mutant adenovirus, dl753, produced higher levels of ADP than rec700, which produces wild-type levels of ADP. Wold I, ¶5, citing to pages 18-20 of Exhibit A.
- The inventors conducted immunofluorescence assays that confirmed that E3 deletion mutants (dl732 and dl753) produced more ADP than wild-type adenovirus. Wold I, ¶5, citing to pages A21-A25 of Exhibit A. Thus, it was found that overexpression of ADP compared to wild-type adenovirus was found to be associated with deletions in the E3 region.
- The results of virus release assays conducted by the inventors showed that ADP mutants that had large plaques released more virus than both wild-type Ad and ADP mutants that had small plaques. Wold I, ¶5, citing to page A26 of Exhibit A. Thus, the inventors found that overexpression of ADP promoted cell death in infected cells.
- To further pursue their studies pertaining to adenoviruses that overexpress ADP, the inventors submitted a proposal, entitled "Adenovirus E3-11.6K Protein as a Cell Death-Promoting Agent" to Chiron Corp. Wold I, ¶5, citing to Exhibit B. In the proposal, the inventors reviewed their earlier studies, and concluded that "[s]ince the 11.6K protein [ADP] can promote the cell death of adenovirus-infected, it has the potential use as a therapeutic agent to kill cells, e.g., malignant cell, in humans." Wold I, ¶5, and Exhibit B of Wold I, page 3; see also page 6 *et seq.* for a discussion as to how the ADP gene might be applied in human therapy. Thus, the proposal addressed application of adenoviral vectors that overexpress ADP in the treatment of cancer in humans.

- The proposal discusses at length the construction of nondefective (replication competent) vectors. The KD/GZ class of adenovirus vectors are described in the proposal, where it is stated that "[t]he nondefective vectors generally have the E3 transcription unit deleted and replaced with the transgene" [ADP]. Wold I, Exhibit B, page 4 of proposal. The construction of a vector deleted in the E1A, E1B and E3 regions, wherein the ADP gene is reinserted in an expression cassette driven by the CMV promoter is discussed. Wold I, Exhibit B, page 6, second full paragraph. The proposal suggests the preparation of vectors that "optimize expression" [*viz*, "overexpress"] of the ADP gene, and mention the possibility of preparing "nondefective" vectors (that is, replication competent vectors). Wold I, Exhibit B, page 8.
- 11.6K [ADP] overexpression and studies to evaluate the effects of overexpression of ADP are discussed in the proposal. Wold I, Exhibit B, page 7.
- In section C.3. of the proposal, beginning on page 7, it is alternatively proposed to test the ability of an ADP expressing vector to overexpress the ADP gene (*i.e.*, the 11.6K gene) during early stages of infection by constructing a vector into which the "11.6K gene will be built in" yet which lacks all other E3 region genes and which contains all other adenovirus genes." The concept that deletion of the E3 transcription unit and insertion of the ADP gene would result in overexpression is based on the understanding that deletion of most or all of the E3 genes other than the ADP gene facilitates overexpression of ADP mRNA by reducing competition for splicing of the major late pre-mRNAs, a concept with is discussed in the proposal at page 7. Wold I, ¶5, citing to page 7 of Exhibit B. Thus, the proposal

discusses the construction of replication competent adenoviruses that overexpress ADP, and their application in the treatment of cancer in humans.

- Applicants have also submitted evidence that prior to March 3, 1997, the present inventors constructed a recombinant adenovirus vector (KD1) that is replication-competent in neoplastic cells and that overexpresses ADP. Wold I, ¶6, citing to Exhibits D1-4, E1-10, I1-I31, F1-F8, D39, C6, C9, D48-49, and D47, D52, and C16.

Thus, Appellants have set forth evidence demonstrating that the present inventors constructed a replication-competent ADP overexpressing vector prior to March 3, 1997, the earliest priority date of Henderson/Little. Further, Appellants have set forth evidence that they conceived of the idea that replication-competent ADP overexpressing adenoviral vectors can be applied in the treatment of human cancer prior to March 3, 1997.

Further, in March, April and May of 1997, and inventors conducted studies on KD1 on virtually every day during those months. See Appeal Brief, page 19, citing to page 8 of Wold I under the headings "5/9/97 – 5/23/97" and "5/13/97 – 6/2/97." *Id.* Those studies confirmed that KD1 overexpressed ADP relative to wild-type levels. Furthermore, the Wold II declaration demonstrates the successful testing of KD1 in an animal having cancer shortly after these confirmatory studies. See Appeal Brief, page 19-23, citing to Wold II.

***(2) Appellants' Evidence of Conception is Sufficient Under In re Stempel***

The law is clear that a Rule 131 declaration need only show so much as the prior art discloses. *See, e.g., In re Stempel*, 113 U.S.P.Q. 77 (CCPA 1957). Under the doctrine of *In re Stempel*, it is submitted that the Little/Henderson references have been antedated inasmuch as the Rule 131 showing is at least commensurate in scope with that found in the March 1997 and

March 1998 respective filing dates of the Henderson and Little patents. In particular, as discussed above, Appellants have constructed a replication competent adenoviral vector (KD1) that overexpresses ADP for use in cancer therapy. Further, neither Henderson nor Little conducted studies demonstrating that any vector set forth therein actually overexpressed ADP. Therefore, Appellants are not required to set forth evidence of such studies in order to overcome Henderson and Little as prior art under Rule 131. The Board has affirmed the Examiner's rejection of the claims as being inherently anticipated by Henderson and Little. In view of the foregoing, it is respectfully submitted that Appellants have shown at least as much as Henderson and Little, and that the Wold I and Wold II declarations are sufficient to overcome Henderson and Little as prior art.

***b) The "Structural Claims": Claims 60, 61, 64-66, 68, 69, 72-75, 97-99, and 107***

The "structural claims" pertain to methods for treating a cancer in an animal having a tumor, the method comprising administering to the tumor an adenovirus vector that is replication-competent in neoplastic cells and ***expresses*** an adenovirus death protein, wherein the adenoviral vector includes one or more of the structural features set forth in claim 60. These structural features include (1) the ADP is expressed from an ADP coding sequence positioned under the control of a promoter other than the endogenous promoters for ADP; (2) the adenovirus vector comprises a deletion in the E3 region that removes a splice site for an E3 mRNA; (3) the ADP is expressed from an ADP coding sequence flanked by a pre-mRNA splicing and cleavage/polyadenylation signal other than the pre-mRNA splicing and cleavage/polyadenylation signal normally associated with the ADP gene; and/or (4) the ADP is expressed from an ADP coding sequence that is positioned downstream of the coding sequence for another adenovirus mRNA, together with a sequence on the 5' side of the ADP coding

sequence that allows for internal initiation of translation of ADP. The structural claims, unlike the "overexpress ADP" claims, ***do not require overexpression of ADP***.

As an initial matter, Appellants note that the Examiner has not addressed whether the evidence of record supports conception of the structural claims prior to March 3, 1997, and thus appears to concede that the evidence of record is sufficient to support conception of the structural claims. The Examiner's Answer does not comment on the sufficiency of the evidence pertaining to when it was known or appreciated that an adenovirus with a structural feature as claimed expressed ADP and was useful for treating cancer.

Appellants, as set forth above, have set forth substantial evidence which shows that prior to the earliest priority date of Henderson/Little, the present inventors had conceived of the idea of preparing vectors with E3 deletions plus reinsertion of the ADP gene for the purpose of testing overexpression of ADP and for the purpose of developing a cancer therapeutic. Although the present inventors provided evidence that their vectors overexpressed ADP, they were not required to do so since the structural claims do not require a vector that overexpresses ADP. The fact that the structural claims do not require overexpression renders irrelevant the Examiner's argument that KD1 was not shown to overexpress ADP prior to March 3, 1997. Therefore, Appellants have demonstrated evidence of conception sufficient to meet the standard under Rule 131.

### 2. Appellants' Evidence of Conception is Sufficient to Meet the Standard Set Forth in *Invitrogen v. Clontech*

The only argument set forth by the Examiner in the Supplemental Examiner's Answer is that Appellants' evidence of conception is insufficient to meet the standard set forth in *Invitrogen v. Clontech*, a case which was decided after Appellants had filed their appeal brief, because Appellants did not actually conduct testing to confirm that KD1 actually overexpressed ADP

until after March 3, 1997, the earliest priority date of Henderson/Little. *Invitrogen v. Clontech*, 77 U.S.P.Q. 2d 1161, 1168 (Fed. Cir. 2005).

As discussed above, Appellants have set forth substantial evidence that prior to March 3, 1997, the present inventors conceived of replication-competent adenoviral vectors that overexpress ADP, and their application in the treatment of cancer in humans.

Further, as discussed above regarding *In re Stempel*, Appellants are not required to set forth any evidence of studies to confirm that KD1 actually overexpressed ADP because they have shown at least as much as Henderson and Little. *In re Stempel*, 113 U.S.P.Q. 77 (CCPA 1957). Therefore, the Examiner's assertion is incorrect.

Appellants also note for the record that the facts of *Invitrogen* are distinguishable from the present case. In *Invitrogen*, the patent at issue pertained to a genetically modified enzyme, reverse transcriptase (RT) with DNA polymerase, but no RNase H activity. *Invitrogen*, 77 U.S.P.Q. 2d at 1164. The patentee altered a gene that originally encoded wild or natural RT, resulting in a mutant enzyme with the desired properties. *Id.* The primary issue was whether Columbia University researcher Dr. Goff had conceived of a similar invention of RT before the patentee, and was diligent in reducing it to practice after the patentee's first reduction to practice in 1987. 77 U.S.P.Q. 2d at 1164-1165. In *Invitrogen*, Dr. Goff had roughly 100 mutants under examination. 77 U.S.P.Q.2d at 1164. The court conducted an analysis of the evidence pertaining to when Dr. Goff appreciated his invention. 77 U.S.P.Q.2d at 1170-1172. The Court, in holding that the district court erred in granting partial summary judgment establishing Goff's conception before January 27, 1987, held that there was insufficient evidence of record to support conception. 77 U.S.P.Q.2d at 1172. In particular, the Courts found that the record did

not show that Goff set out to create RNase H minus RT, or that he recognized his invention before the priority date. 77 U.S.P.Q.2d at 1170.

In contrast, in the present case (as summarized above), Appellants constructed a ***single vector*** for application in cancer therapy: KD1. The present inventors recognized the significance of ADP overexpression in their early work, submitted a research proposal, and conducted experiments test their recombinant vector for ADP overexpression. In contrast, the facts in *Invitrogen* fail to set forth any such chain of appreciation of the invention and its significance.

In view of the foregoing, it is respectfully submitted that Appellants have set forth substantial evidence demonstrating appreciation and thus conception of the invention prior to March 3, 1997.

### *3. Following Conception, Appellants Were Diligent in Reducing the Claimed Invention to Practice*

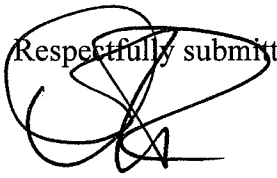
Since the Examiner did not argue that Appellants have not set forth sufficient evidence to show that the inventors were diligent in reducing the invention to practice, Appellants will assume that the Examiner has accepted their evidence of record. This evidence is summarized on pages 19-23 of the appeal brief. Therefore, in accordance with 37 C.F.R. §1.131, it is respectfully submitted that Appellants have demonstrated that the present inventors conceived of the claimed invention prior to the earliest priority date of Henderson and Little, and were diligent in reducing their invention to practice.

## CONCLUSION

In view of the foregoing, it is respectfully submitted that the two declarations set forth by Appellants (Wold I and Wold II) are sufficient under 37 C.F.R. §1.131 to establish invention of the subject matter of the appealed claims prior to the effective filing date of Henderson and Little. It is respectfully submitted, in light of the above, none of the appealed claims are properly rejected.

Therefore, Appellants request that the Board reverse the pending grounds for rejection.

Respectfully submitted,



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